PATENT

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8/2/06 Michelle Hobson

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: S. Zhou
WOLFFE et al.	Group Art Unit: 1631
Serial No.: 10/083,682	Confirmation No.: 1541
Filing Date: October 24, 2001	Customer No.: 20855
Title: LIBRARIES OF REGULATORY SEQUENCES; METHODS OF MAKING AND USING SAME (as amended)	

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing in response to the Notification of Non-Compliant Appeal Brief mailed July 10, 2006, please find the following documents:

x Appeal Brief (19 pages) with attached Claims Appendix (3 pages), Evidence Appendix (1 page) and Related Proceedings Appendix (1 page)

x Return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	10	- 124	0	x $50.00	$0
Independent Claims	1	- 23	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Appeal Brief Fee					$0
Small Entity Reduction (if applicable)					$0
TOTAL FEE DUE					$0

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: August 2, 2006

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USSN 10/083,682
8325-0015.20
S15-US2

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:

A.P. Wolffe *et al.*

Application No.: 10/083,682

Filed: October 24, 2001

For: LIBRARIES OF REGULATORY SEQUENCES, METHODS OF MAKING AND USING SAME (as amended)

Examiner: S. Zhou

Group Art Unit: 1631

Confirmation No.: 1541

APPEAL BRIEF

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TABLE OF CONTENTS

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: A.P. Wolffe *et al.* Application No.: 10/083,682 Filed: October 24, 2001 For: LIBRARIES OF REGULATORY SEQUENCES, METHODS OF MAKING AND USING SAME (as amended)	Examiner: S. Zhou Group Art Unit: 1631 Confirmation No.: 1541

APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

INTRODUCTION

A brief on appeal was submitted on October 6, 2005. An Examiner's Answer was mailed on January 12, 2006 and a Reply Brief was submitted on March 9, 2006. In an Order Returning Undocketed Appeal to Examiner dated June 9, 2006, the Board of Patent Appeals and Interferences returned the application to the Examiner, requiring correction of the Appeal Brief filed October 6, 2005 because the "Summary of the Claimed Subject Matter" appearing on pages 3-4 did not map the claimed invention to the independent claims, as set forth in 37 C.F.R. §

41.37(c)(1)(v). The Examiner mailed the Board's Order and a Notification of Non-Compliant Appeal Brief on July 10, 2006. Accordingly, a revised Appeal Brief filed by August 10, 2006 is timely filed. As before, all claims were finally rejected under 35 U.S.C. §§112 (1st paragraph) and 103 in a Final Office Action mailed March 31, 2005.

I. REAL PARTY IN INTEREST

Sangamo BioSciences, Inc., the assignee of record of the above-referenced patent application is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellants have appealed the final rejection of all claims in parent application USSN 09/844,501. Appellant is not aware of any related interferences or judicial proceedings.

III. STATUS OF THE CLAIMS

Claims 66-71 and 125-128 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on October 24, 2001 with claims 1 to 124. Claims 1 to 124 were subject to a Restriction Requirement and, in an Amendment filed December 8, 2004, claims 1-65 and 72-124 were canceled; claims 66-71 were amended; and new claims 125-128 were presented. Claims 66-71 and 125-128 have not been amended since. Accordingly, claims 66-71 and 125-128 are pending as shown in the Claims Appendix. All pending claims remain rejected under 35 U.S.C. § 112, 1st paragraph (written description) and 35 U.S.C. § 102(b).

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed March 31, 2005, Appellant filed a Response on May 24, 2005. No amendments to the claims were made in that response. An Advisory Action was mailed on June 21, 2005 reiterating the rejections as set forth in the

Final Office Action. Thus, all claims remained rejected for the reasons set forth in the Final Office Action.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter relates to polynucleotides corresponding to accessible regions of cellular chromatin and libraries of these polynucleotides. Although previously it had been possible to identify accessible regions in cellular chromatin (*i.e.*, regions not packaged in a typical nucleosomal structure), the process of identification (*i.e.*, by nuclease digestion) destroyed these sequences. Accordingly, it was previously not possible to isolate such accessible sequences. Unlike libraries made from naked DNA (which are representative of all DNA sequences present in the chromatin of the cell), the presently claimed subject matter provides polynucleotides and libraries that consist essentially of DNA sequences corresponding to a subset of the DNA sequences present in the chromatin of a cell, namely accessible regions of cellular chromatin.

In particular, independent claim 66 is drawn to a polynucleotide that is a member of a library of polynucleotides (page 8, lines 4-5; page 47, line 25 to page 55, line 20). Each member of the library comprises a vector and an insert in the vector (page 47, lines 30-33). The insert sequences consist essentially of accessible regions of cellular chromatin (page 47, lines 26-33). Moreover, independent claim 66 also recites that the library is obtained according to the method of: (a) contacting cellular chromatin with a probe, wherein reaction of the probe with cellular chromatin results in polynucleotide cleavage at accessible regions of cellular chromatin (page 4, line 29 to page 5, line 6); (b) deproteinizing the cleaved chromatin of step (a) (page 6, lines 14-17; page 51, lines 21-23; page 113, lines 11-14; page 123, lines 22-24); (c) digesting the deproteinized chromatin of step (b) with a nuclease to generate a collection of polynucleotide fragments (page 51, lines 21-23; page 123, lines 26-30); and (d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage (page 51, lines 31-34; page 124, lines 4-14).

The method recited in claim 66 results in production of a library in which each insert contains sequences derived from a region that was accessible in the chromatin of the cells from which the library was obtained. Certain of the inserts may additionally contain sequences that flanked those that were accessible in the cellular chromatin (*e.g.*, page 28, lines 1-5). Thus, each insert consists essentially of DNA sequences that were accessible in the chromatin of the cell from which the library was obtained, *i.e.*, accessible sequences. Since accessible sequences often play a role in transcriptional regulation (page 27, lines 4-6; page 29, line 28 through page 30, line 3; page 30, lines 15-16), the library is enriched in DNA sequences which served a regulatory function in the cells from which the library was obtained (page 30, lines 3-4).

Dependent claim 67 is drawn to a library comprising a plurality of the polynucleotides recited in independent claim 66 (page 47, lines 26-29). Dependent claim 68 specifies that the cellular chromatin from which the polynucleotides of the library of dependent claim 67 are obtained may itself be obtained from cells at a particular stage of development (page 8, lines 11-14). Dependent claim 69 specifies that the cellular chromatin is obtained from a particular tissue, and dependent claims 70 and 71 specify, respectively, that the cellular chromatin is obtained from diseased cells and infected cells (page 8, lines 11-14).

Dependent claim 125 indicates that the probe that reacts with cellular chromatin, to obtain the polynucleotides as described in independent claim 66, is a nuclease (page 5, line 31), and dependent claims 126 and 127 specify that the nuclease is a restriction enzyme (claim 126) or a plurality of restriction enzymes (claim 127) (page 6, line 15).

Dependent claim 128 specifies that the deproteinized chromatin of step (c) of independent claim 66 is digested with a restriction enzyme (page 6, lines 16-17).

VI. GROUNDS OF REJECTION

1. Claims 66-71 and 125-128 stand rejected under 35 U.S.C. 112, 1st paragraph as allegedly not adequately described by the specification as filed.

2. Claims 66-71 and 125-128 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by pages 177-183 of the Clontech Catalog (hereinafter "Clontech").

VII. ARGUMENTS

1. The Specification Describes the Claims on Appeal

Claims 66-71 and 125-128 remain rejected under 35 U.S.C. § 112, first paragraph as allegedly not described by the specification as filed. In support of the rejection, the Advisory Action stated (pages 3-4):

> While it is true that the claims and disclosure in Regents of the Univ. Calif. v. Eli Lilly are different from those in the instant application, it is in the same state of art: novel nucleic acids and/or polypeptides. Moreover, the fact patterns in both cases are similar in that they both claim nucleic acids and/or polypeptides whose sequences are not disclosed. Thus, the court decision in Regents of the Univ. Calif. v. Eli Lilly applies to this case. The sequences of SEQ ID NOs:10, 11, and 12 are not representative of all the species of [the] claimed genus.

Thus, it was alleged that, as in the *Eli Lilly* case, the specification at hand fails to describe sufficient representative species to describe the claimed genus of libraries.

Appellant submits that there is ample description in the specification regarding libraries and polynucleotides as claimed and there is no requirement that specific sequences exemplified in the specification be recited in the claims. As such, the written description requirement of 35 U.S.C. § 112, first paragraph has been satisfied.

(a) The Holding in *Eli Lilly* Is Not Relevant To The Case At Hand

For the reasons of record, the Office's reliance of *Regents of the Univ. Calif. v. Eli Lilly* remains misplaced. The written description requirement of § 112 is highly fact-dependent and, contrary to the statements in the Advisory Action, the claims, disclosure and state of the art in *Eli Lilly* are entirely different from those in the case at hand.

First, the claims in the pending case are product-by-process claims whereas the claims in *Eli Lilly* were directed to polynucleotides *per se*. Further, the disclosure in Appellant's case includes actual exemplification of the products (polynucleotides such as SEQ ID NOs:10, 11 and 12) obtained by the recited process steps. *See, e.g.,* Example 15, pp. 123-126. In contrast, the disclosure in the *Eli Lilly* case did not describe either the isolation or the sequence of the claimed product (human insulin cDNA).[1] Finally, the relevant state of the art in each case is entirely different -- making libraries of non-coding sequences (accessible regions) prepared by recited, described and exemplified method steps (Appellant) versus obtaining novel coding sequences (*Eli Lilly*).

Thus, because the claims, disclosure and relevant state of the art in *Eli Lilly* are entirely different from the claims, disclosure and relevant state of the art case on appeal, the Federal Circuit's holding in *Eli Lilly* is not relevant to the question of whether the written description requirement is fulfilled for the subject matter of the appealed claims.

(b) The Claims Are Drawn to Polynucleotides And Libraries Fully Described By The Specification As Filed

It is well-settled law that the fundamental factual inquiry in written description is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed. *See, e.g., Vas Cath, Inc. v. Mahurkar*, 935 F.2d 1557, 19 USPQ2d 1111. Determining whether the written description requirement is satisfied is a question of fact and the burden is on the Examiner to provide evidence as to why a skilled artisan would not have recognized that the applicant was in possession of the claimed invention at the time of filing. *Vas Cath, Inc. v. Mahurkar*, 19 USPQ2d 1111 (Fed. Cir. 1991); *In re Wertheim*, 191 USPQ 90 (CCPA 1976). It is not necessary that the application describe the claimed invention in *ipsis verba*. Rather, all that is required is

[1] Therefore, the Examiner is inaccurate in asserting that this case is like *Eli Lilly* in that no nucleic acid sequences are disclosed. *See,* page 2 of the Advisory Action, reproduced above. In fact, the specification clearly discloses exemplary polynucleotide sequences of accessible regions in the Examples as filed.

that the specification reasonably convey possession. *See, e.g., In re Lukach*, 169 USPQ 795, 796 (CCPA 1971).

The Patent Office Guidelines are in accord and stress not only proper claim construction prior to analysis, but also indicate that the written description requirement is highly fact-dependent and there is a strong presumption that an adequate written description of the claimed invention is present at the time of filing (Final Examiner Guidelines on Written Description, 66 Fed. Reg. 1099).

Thus, any written description inquiry must begin with proper claim construction. Here, the claims on appeal are not drawn to any and all polynucleotides having any sequence. In fact, the genus encompassed by the claims on appeal is nowhere near as broad as that painted by the Examiner. It is simply those sequences, in the chromatin of a given cell, that are accessible to a probe.

Even claims 66 and 125-128, which as noted in the Advisory Action, are directed to "a" polynucleotide, clearly indicate that the claimed polynucleotide is a member of a library of accessible regions of cellular chromatin. By definition, a library contains a number of different sequences, and, as is well known to those of skill in the art of molecular biology, it is impossible to predict the identity of the sequences that will be obtained after construction of a library.[2]

Thus, conception of the claimed polynucleotides libraries does not, indeed cannot, require description of the nucleotide sequence of every member of the library. Satisfaction of the written description does not require a showing that the skilled artisan can predict *a priori* each and every nucleotide sequence falling within the scope of the claims, but, rather, a demonstration that one of skill in the art would be aware an applicant was in possession of methods for making libraries of accessible regions of cellular chromatin, and of the libraries obtained through the practice of those methods. Here, the skilled artisan, having followed the teaching of the specification, would have no doubt that Appellant was in possession of a sequence corresponding to an accessible region of cellular chromatin, or to a library of such sequences.

[2] This fact points to yet another reason why the decision in *Eli Lilly* is not applicable to the present case: in *Eli Lilly*, it was possible for the inventors to identify the sequence they were trying to claim.

Furthermore, the claimed polynucleotides must not only correspond to accessible regions of cellular chromatin, they must have been obtained using the particularly specified method, which results in isolation of such accessible regions. Thus, the claims at issue are product-by-process claims and, as such, are subject to a written description test much different from that used for product claims (including those in *Eli Lilly*) (*see,* M.P.E.P. § 2163):

> ...where the process has actually been used to produce the product, the written description requirement for a product-by-process claim is clearly satisfied.
>
> With respect to claims 66 and 125-128, the product is a polynucleotide which is a member of a library. Example 15 describes three such products (SEQ ID NOs: 10, 11 and 12) obtained from two different libraries. Thus, when the product-by-process claims on appeal are properly construed, it is plain that they are drawn to a genus of polynucleotide library members that is more than adequately described by the specification as filed. In addition to fully describing the claimed polynucleotides and libraries, Appellant's specification also describes how the process steps recited in the claims have actually been used to produce these polynucleotides and libraries.[3] Thus, the rejection of the pending product-by-process claims is improper.

(c) Disclosure Of A Single Species Can Satisfy The Written Description Requirement

As noted above, the Examiner also errs in asserting that insufficient representative species are disclosed. As noted above, sequences are in fact exemplified and these exemplified sequences are more than representative of the genus encompassed by the claims. The flexibility and wide applicability of the claimed compositions should not be used as a basis for asserting that they are incompletely described; and any requirement for Appellants to actually provide more examples of such polynucleotides than already described is unnecessary for compliance with the written description requirement; moreover, limitation of the claimed subject matter to

[3] Although the sequences of a large number of additional members of the libraries described in Example 15 were obtained by the inventors, their disclosure would have added nothing to the application that was not already provided by the sequences which were disclosed.

the exemplary sequences disclosed in the specification would prevent Appellants from claiming what they believe to be their invention.

Indeed, it is well settled that description of a single species can provide an adequate description, even for a broad genus. Thus, Appellant's disclosure is sufficient to establish that Appellant was in possession of the claimed subject matter at the time of filing.

In this regard, the PTO guidelines on written description include various Examples that establish that disclosure of a single species can more than adequately describe a genus. These Examples were favorably commented on by the Federal Circuit in *Enzo Biochem Inc. v. Gen-Probe Inc.*, 323 F.3d (Fed. Cir. 2002). In particular, Example 10, entitled "Process claim" states the following (underlining added):

> **Claim**:
> Claim 1: A process of producing an isolated polynucleotide comprising hybridizing SEQ ID NO:10 to genomic DNA in 6XSSC and 65°C and isolating the DNA polynucleotide detected with SEQ ID NO:10.
>
> Claim 2: An isolated DNA that hybridizes with SEQ ID NO:10.
>
> **Analysis**:
> ... The specification presents an example where a single species has been reduced to practice, i.e., isolation of SEQ ID NO:11 based on hybridization with SEQ ID NO:10. Therefore the disclosed species within the genus has been adequately described. Now turning to the genus analysis, the art indicates that there is no substantial variation within the genus because of the stringency of hybridization conditions which yields structurally similar molecules. <u>The single disclosed species is representative of the genus</u> because reduction to practice of this species, considered along with the defined hybridization conditions and the level of skill and knowledge in the art, are sufficient to allow the skilled artisan to recognize that applicant was in possession of the necessary common attributes or features of the elements possessed the members of the genus. ...
>
> **Conclusion**:
> Claim 1 is adequately described. ...
>
> **Note: Applicant may overcome the written description rejection of the product by, for example, substituting claim 2 with a product-by-process claim such as the one below.**

Claim 2. *The isolated DNA polynucleotide prepared according to the process of claim 1.*

The written description inquiry for the product-by-process claims on appeal is highly analogous to that of Example 10, particularly the Patent Office's indication that product claim 2 of Example 10 would be adequately described if rewritten in product-by-process format to include novel process steps. In the case on appeal, all of the claims are already in product-by-process form, using a novel process that allows for the isolation of sequences corresponding to accessible regions from cellular chromatin. Further, the art indicates that it was conventional at the time of filing to make libraries by inserting polynucleotide sequences into a vector backbone. In other words, the specification's clear description (and indeed exemplification) of the unconventional elements of the claimed subject matter, namely the novel process steps, is more than ample to indicate satisfaction of the written description requirement by evincing possession at the time of filing.

Moreover, a person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because of the requirement in the claims that the library inserts consist essentially of accessible regions and because of the requirement that specific process steps be used to obtain these polynucleotides and libraries. Therefore, it would be expected that the claimed (novel) process steps would yield polynucleotides corresponding to accessible regions. Accordingly, a representative number of species is disclosed, in view of the novelty of the process steps and the high level of skill and knowledge in the art.

Like Example 10, Example 18 of the PTO Guidelines, entitled "Process claim where the novelty is in the method steps" also illustrates a fact pattern that is highly instructive in the pending case (Example 18, underlining added):

> **Specification**: The specification teaches a method for producing proteins from mitochondria from the fungus *Neurospora crassa*. In the method, mitochondria are isolated from this fungus and transformed with a mitochondrial expression vector which comprises a nucleic acid encoding a protein of interest. The protein is subsequently expressed, the mitochondria [ ] lysed, and the protein

is isolated. The specification exemplifies the expression of β-galactosidase using the claimed methods using a cytochrome oxidase promoter.

Claim:

1. A method of producing a protein of interest comprising:
obtaining *Neurospora crassa* mitochondria,
transforming said mitochondria with an expression vector comrpising a nucleic acid that encodes said protein of interest,
expressing said protein in said mitochondria, and
recovering said protein of interest.

Analysis:

...A search of the prior art reveals that the claimed method of expression in *Neurospora crassa* is novel and unobvious. ...

There is actual reduction to practice of a single embodiment, i.e., the expression of β-galactosidase.

The art indicates that there is no substantial variation within the genus because there are limited number of ways to practice the process steps of the claimed invention.

The single embodiment is representative of the genus based on the disclosure ... considered along with the level of skill and knowledge in the gene expression art. One of skill in the art would recognize that applicant was in possession of all of the various expression methods necessary to practice the claimed invention.

Conclusion: The claimed invention is adequately described.

As with Example 10, the claim, analysis and conclusion set forth in PTO Example 18 are also directly relevant and analogous to the written description analysis in the pending case. In particular, the pending product-by-process claims are analogous to the process claim presented in PTO Example 18 in that they recite a novel process (method of expression in Example 18 and method of isolating accessible regions in the claims on appeal) and include actual reduction to practice.

Thus, actual reduction to practice of a single disclosed species is more than sufficient to satisfy the written description requirement in the case at hand because, as in PTO Examples 10 and 18, the process steps are novel. Put another way, a person having ordinary skill in the art would conclude that applicant was in possession of all of the various polynucleotides and libraries obtained from the methods recited in the claims.

There is absolutely no requirement that Appellant describe each and every polynucleotide member of a library as claimed. Rather, the test is whether the specification contains sufficient disclosure to convey possession of the claimed subject matter. For the reasons of record, reiterated herein, the specification as filed, in view of the state of the art, more than adequately describes the claimed polynucleotides and libraries.

2. Anticipation Has Not Been Established

In the Advisory Action, the rejection of all pending claims are allegedly anticipated by the Clontech catalog was reiterated (Advisory Action, page 2):

> In regard to the rejection of claims 66-71 and 125-128 under 35 U.S.C. § 102(b) as being anticipated by Clontech ..., applicants' argument is on the ground that member of the Clontech libraries do not comprise an insert that consists essentially of accessible regions. This not deemed persuasive because as set forth in the previous Office Action, the phrase "consists essentially of" is interpreted as being open to unlisted ingredients. In this case, it is open to nucleotides from inaccessible regions. As also set forth in the previous Office Action, the Clontech libraries are made by a method involving digesting the whole genomes of the chromatin of different organisms ... . It would be readily apparent to one of skill in the art that the libraries produced by such a method inherently comprise clones that have an insert that either consists of polynucleotides from regions of cellular chromatin that are accessible .... the use of the phrase "consist essentially of" in the claims indicates that [the] claims are open to such [inaccessible] polynucleotides.

In other words, the Examiner asserts that Clontech's libraries, which are made from a completely different process than that recited in the pending claims, would somehow inherently produce polynucleotides that correspond to accessible regions and libraries that consist

essentially of such polynucleotides. Such assertions are not supported by any evidence and are untenable.

(a) The Transition Phrase "Consisting Essentially Of" Cannot Be Interpreted As Being Open to Any Unlisted Ingredient

The assertion that the transitional phrase "consisting essentially of" renders the claims open to the inclusion of inaccessible regions is contrary to basic tenets of claim drafting and claim construction. See, for example, MPEP 2111.03:

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. . . . For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." (citations omitted, emphasis in original)

In the case at hand, the basic and novel characteristics of the claimed polynucleotides and libraries are that they arise from, and correspond to, accessible regions of cellular chromatin. These basic and novel characteristics are recited in independent claim 66, both in the preamble and in step (a), in which it is recited that cellular chromatin (not naked cellular DNA) is contacted with a probe.

Thus it is clear that the claimed subject matter is directed to polynucleotides that consist essentially of accessible regions of cellular chromatin (and libraries of these polynucleotides). Clearly, the phrase "consists essentially of" in the present context would not read on polynucleotides corresponding to inaccessible regions, as such polynucleotides are not "unspecified" but would materially affect the basic and novel characteristic of the claimed polynucleotides.

Thus, the Examiner errs in concluding that the claims read on polynucleotides corresponding to both accessible and inaccessible regions. The language of the claims

themselves indicates that polynucleotides corresponding to inaccessible regions are not the claimed subject matter.

(b) Clontech Does Not Expressly Or Inherently Disclose Each And Every Element Of the Pending Claims

It is also error to assert that Clontech discloses, expressly or inherently, the elements of the pending claims.

As previously pointed out by Appellants, the Clontech catalogue discloses nothing more than genomic libraries obtained by digestion of naked DNA.[4] Although the Examiner has asserted that the Clontech libraries are obtained by digestion of chromatin[5], he has provided absolutely no evidence to support such an allegation.

Plainly, Clontech does not expressly describe or demonstrate (1) a polynucleotide member of a library including inserts consisting essentially of accessible regions of cellular chromatin; (2) contacting cellular chromatin with a probe that cleaves the cellular chromatin at accessible regions of cellular chromatin; and/or (3) deproteinizing the cleaved cellular chromatin -- essential elements of each and every pending claim.[6] Rather, Clontech describes a library (and library members) made from naked DNA, a substance that is very different from cellular chromatin. By no stretch of the imagination could digestion of naked DNA, under any circumstances, possibly produce a library of polynucleotides consisting essentially of accessible regions, as claimed. Rather, it produces a collection of polynucleotides representative of the entire genome and therefore consisting of both accessible and inaccessible sequences. Furthermore, inasmuch as naked DNA is devoid of associated proteins (*i.e.*, it is not chromatin), Clontech cannot possibly teach the deproteinizing step required by the claims on appeal.

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[4] See, *e.g.*, Responses dated December 8, 2004 and May 24, 2005

[5] See, *e.g.*, Office Action dated September 9, 2004 at page 12; Office Action dated March 31, 2005 at page 8 and Advisory Action dated June 21, 2005 at page 2

[6] In fact, the Examiner acknowledges Clontech's failure to expressly disclose the claimed subject matter inasmuch as the rejection is based solely on alleged inherent disclosure.

Accordingly, Clontech fails to expressly teach each and every claim element and, therefore, cannot expressly anticipate any of the appealed claims.

Nor does the Clontech catalog inherently anticipate the claims on appeal. As previously noted, inherency cannot be established by probabilities or possibilities, and the burden is on the Office to provide factual and technical grounds establishing that the inherent feature necessarily flows from the teachings of the reference *See, e.g., Continental Ca Co. USA, Inc. v. Monsanto Co.* 20 USPQ2d 1746, 1749 (Fed. Cir. 1987). This is true with regard to structural, functional and process limitations. Indeed, as the Board of Patent Appeals and Interferences and Federal Circuit have repeatedly established, "the examiner must provide some evidence or scientific reasoning to establish the reasonableness of the examiner's belief that the functional limitation is an inherent characteristic" of the reference. *Ex parte Skinner,* 2 USPQ2d 1788 (BPAI 1986), emphasis added.

The Office has provided no such evidence or reasoning, but, instead, has merely asserted that the cited reference, disclosing a genomic library, inherently discloses the particularly claimed subject matter.

In reality, as noted in the record and above, digestion of naked DNA (as described in Clontech) will necessarily result in a collection (library) of DNA fragments that include both accessible and nonaccessible regions, as there are no proteins in naked DNA to protect any sequences from digestion. By contrast, the claimed libraries are composed of fragments from accessible regions, as they are made from digestion of cellular chromatin, in which chromosomal proteins protect non-accessible regions from digestion. The recited process steps thus impart structural and functional characteristics that fully distinguish the claimed polynucleotides from those of Clontech. Plainly, because a library consisting essentially of accessible regions and prepared from cellular chromatin as claimed is **not** an inherent feature of Clontech's libraries, the Clontech catalog does not anticipate the pending claims.

Thus, Clontech fails to describe, expressly or inherently, polynucleotides and libraries as claimed. Therefore, Appellant submits that the rejection cannot be sustained and should be withdrawn.

CONCLUSION

For the reasons stated above, Appellant respectfully submits that the specification adequately describes the pending claims and that the pending claims are patentable over the art cited by the Examiner. Accordingly, Appellant requests that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: August 2, 2006

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CLAIMS ON APPEAL

1 to 65. (canceled).

66. (previously presented) A polynucleotide, wherein the polynucleotide is a member of a library of polynucleotides, the members of the library comprising a vector and an insert, wherein the insert sequences consist essentially of accessible regions of cellular chromatin, wherein the library is obtained according to the method of:

(a) contacting cellular chromatin with a probe, wherein reaction of the probe with cellular chromatin results in polynucleotide cleavage at accessible regions of cellular chromatin;

(b) deproteinizing the cleaved chromatin of step (a);

(c) digesting the deproteinized chromatin of step (b) with a nuclease to generate a collection of polynucleotide fragments; and

(d) selectively cloning polynucleotide fragments comprising one end generated by probe cleavage.

67. (previously presented) A library comprising a plurality of polynucleotides according to claim 66.

68. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from cells at a particular stage of development.

69. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from cells of a particular tissue.

70. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from diseased cells.

71. (previously presented) The library of claim 67, wherein the cellular chromatin is obtained from infected cells.

72 to 124. (canceled).

125. (previously presented): The polynucleotide of claim 66, wherein, in step (a), the probe is a nuclease.

126. (previously presented): The polynucleotide of claim 125, wherein the nuclease is a restriction enzyme.

127. (previously presented): The polynucleotide of claim 126, wherein the probe comprises a plurality of restriction enzymes.

128. (previously presented): The polynucleotide of claim 66, wherein, in step (c), the nuclease is a restriction enzyme.

RELATED PROCEEDINGS APPENDIX

As noted above on page 2 of this Brief on Appeal and pursuant to 37 C.F.R. § 41.37(c)(i) and (c)(x), Appellant has filed an Appeal Brief in USSN 09/844,501, which is the parent of the instant application. In as much as no decisions have been rendered by a court or the Board in this related case, no documents are submitted with the Related Proceedings Appendix.